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Imperial College  
London SW7 2AZ  
United Kingdom

Patents ADP number (if you know it)

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7409436002

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## 4. Title of the invention

METHOD OF TREATMENT

## 5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

ERIC POTTER CLARKSON  
PARK VIEW HOUSE  
58 THE ROPEWALK  
NOTTINGHAM  
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## METHOD OF TREATMENT

The present invention relates to a method of treatment of cachexia. Cachexia is a severe complication of several chronic diseases, including chronic heart failure (CHF), malignant cancer, acquired immunodeficiency syndrome, thyrotoxicosis and rheumatoid arthritis. The prognostic importance of wasting is well established in several of these conditions [<sup>1,2,3</sup>]. In a single-center study with a total of 171 CHF patients, we documented for the first time that weight loss in CHF is linked to impaired survival independently of other well recognised risk factors (e.g. New York Heart Association [NYHA] functional class, peak oxygen consumption, and left ventricular ejection fraction [LVEF]) [<sup>4</sup>]. Although prospective in design, this study was of limited size, the definition of cardiac cachexia employed (>7.5% documented weight loss) was arbitrary, and it was performed in a research-oriented tertiary referral center with potentially highly selected patients. To date it is not known how frequently significant weight loss occurs in a large unselected population of CHF patients, and when occurring what prognostic impact it carries. It seems logical to define the presence of wasting on the basis of documented weight loss [<sup>5</sup>]; the degree of weight loss best linked to impaired survival is not known.

Multiple physiological pathways are disordered in CHF, and a series of vicious cycles have been described that could transform cardiac abnormalities into hemodynamic, endocrine, immunological, and muscular abnormalities that all could, in the turn, contribute to the clinical picture of chronic heart failure [<sup>6,7,8,9</sup>]. The relative contributions of these very different pathways may vary - not only from patient to patient, but also with each individual over time. The best studied and most widely available treatment option with a positive effect on symptoms and survival of CHF patients is treatment with angiotensin converting enzyme (ACE) inhibitors. It is increasingly evident that ACE inhibitors exert beneficial effects beyond simple hemodynamic effects via a variety of pathways. These include beneficial effects on the neurohormonal axis [<sup>10</sup>] and the endothelium [<sup>11</sup>]. The effect of ACE inhibitors on the development of cachexia is however unknown. The survival benefit of patients with CHF treated with enalapril vs placebo in CONSENSUS [<sup>12</sup>] and vs hydralazine-isosorbide dinitrate in V-HeFT II [<sup>13</sup>] is only significantly achieved in patients with increased catecholamine levels, i.e. in patients with normal levels no significant survival benefit was seen. We have recently

documented [14] that in contrast to peak VO<sub>2</sub>, LVEF, or NYHA class, raised catecholamine levels were closely related to the presence of cardiac cachexia. If ACE inhibitors exert particularly beneficial effects in heart failure patients with raised catecholamine levels, and if these patients are more frequently cachectic, we hypothesised, that the beneficial effect of ACE inhibitors might be linked to a beneficial effect on cardiac cachexia.

To explore these questions and hypotheses, we have performed a re-analysis of the patients treated in the SOLVD treatment trial [15]. To avoid problems related to weight loss due to reduction of edema present at baseline, the results presented here are based on those 2082 patients that were free of detectable peripheral edema at baseline. The reliable quantification of edema is difficult. To avoid biases inherent in estimating weight loss in patients who could also have developed edema we did not adjust for the development of edema during follow-up. Therefore the data presented in this study can be regarded as conservative estimates with regard to the frequency of weight loss, for in the presence of new edema our estimates of weight loss would always be underestimates.

## METHODS

### Patient population

We report on CHF patients who participated in the SOLVD treatment trial [15]. The SOLVD treatment study was a randomized, double blind, and placebo-controlled trial investigating the effects of enalapril treatment in clinically stable patients with a LVEF of 35% or less and evidence of overt congestive heart failure. The precise details of study organisation, inclusion criteria, run-in period (2 to 7 days) and stabilization period (14 to 17 days), randomisation, treatment titration and follow-up have been reported previously [15]. The current re-analysis is restricted to subjects who participated in the SOLVD treatment trial (n=2569), and who had been free of edema at baseline and had survived for at least 4 months thereafter (n=2090). For inclusion into the analysis we also required patients to have weight measurements at baseline

and from at least one follow-up visit at 4 months or later. A further 8 subjects with missing or invalid values for weight measurements had to be excluded. The final number of subjects included in this report is 2082 (81.04% of the original trial population). The baseline clinical characteristics of these 2082 patients were not significantly different from the characteristics of the total study population.

### **Treatment and follow-up**

Of the 2082 patients, 1055 patients were randomised to treatment with enalapril (2.5 to 20mg per day) and 1027 patients to treatment with placebo. The clinical characteristics of these two groups were also similar at baseline (Table 2). During follow-up (range 22 to 51 months), and a total of 756 deaths were observed (36.3%). Body weight at baseline and during follow-up was measured per protocol. Body height was not recorded.

### **Statistical analysis**

Comparison of means between groups was carried out using an unpaired t-test. Comparison of proportions between groups was made by employing the chi-square test. With regards to the definition of the presence of cachexia different, a priori suggested, cut-points [16] of 5.0%, 7.5%, 10.0% and 15.0% weight loss were considered. To address the question of whether or not ACE inhibitors influence the risk of first occurrence of cachexia, we plotted the cumulative incidence of cachexia in the two treatment groups, and analysed it employing the log-rank statistic [17]. In the analysis of first occurrence of cardiac cachexia, at any given follow-up visit, absence of information on cardiac cachexia (i.e. weight not documented at this visit) is treated as censored. The effect of cardiac cachexia on survival is assessed using Cox proportional hazard analysis [16]. For these analyses cardiac cachexia is treated as a time-dependent covariate. The assessment of cardiac cachexia at 4, 8, and 12 months was used in the analysis. These are the time points in the follow-up period with relatively high proportion of complete information on

cachexia status. In the database, information on cachexia status is very sparse towards the end of follow-up, which makes it difficult to assess cardiac cachexia as "truly" time-dependent.

The primary analysis was intention-to-treat. Statistical significance is claimed at a computed p-value <0.05 (two-sided testing). Estimates of effects are provided along with their 95% confidence intervals. Results are adjusted for a priori identified prognostic factors such as age, gender, NYHA functional class, LVEF ( $\leq 25\%$  or  $>25\%$ ), and treatment status (enalapril vs placebo, in the case of assessing the effect of cardiac cachexia on survival).

## RESULTS

Of the 2082 CHF patients in this study, 657 (31.6%) developed  $\geq 7.5\%$  weight loss during follow-up. The cumulative frequency of cardiac cachexia increased continuously over time (Figure 1). The frequency of  $\geq 7.5\%$  weight loss (cross-sectional) at 1 year was 8.5% and it increased to 15.5% (2 years), and 17.2% (3 years). At baseline patients who developed cardiac cachexia with  $\geq 7.5\%$  weight loss during follow-up were 1.3 years older (mean 61.2 vs 59.9,  $p<0.01$ ), had 2.7 kg higher weight (mean 80.5 vs 77.8 kg,  $p<0.001$ ), and they were slightly more frequently treated with diuretics (87.2 vs 82.6%,  $p<0.01$ ) (Table 1). Of the patients in this study, 375 (18.0%) were female. Female CHF patients developed cardiac cachexia more frequently (39.5% vs 29.8% in males for  $\geq 7.5\%$  weight loss,  $p<0.001$ ). Otherwise the baseline clinical characteristics, particularly with regards to NYHA class, LVEF, and disease etiology, of patients who developed cardiac cachexia and those who did not were similar (Table 2). The following clinical characteristics at baseline were independently related to the subsequent development of cardiac cachexia: age (RR 1.05,  $p<0.001$ ), NYHA class I, LVEF, and treatment (0.5).

### Cardiac cachexia and survival

The development of cardiac cachexia was closely related to subsequently impaired survival. All a priori identified competitive cut-points for cardiac cachexia were related to impaired survival - independent of the effects of age, gender, NYHA class, LVEF, and treatment allocation. Of the 756 deaths observed during follow-up, 223 occurred in patients who had been classified as cachectic ( $\geq 7.5\%$  weight loss) at the last visit prior to death, i.e. 29.5% of deaths in CHF patients occurred with cardiac cachexia being present. Amongst different cut-offs for cardiac cachexia between 5 and 15%, weight loss  $\geq 6.5\%$  was the strongest predictor of impaired mortality. The crude effect of cachexia (weight loss  $\geq 6.5\%$ ) on survival was highly significant: RR 1.47 (95% confidence interval: 1.27 to 1.70),  $p=0.00000017$ .

### **Cardiac cachexia and ACE inhibitor treatment**

Patients who were allocated to treatment with enalapril had a significantly lower risk of developing cardiac cachexia during follow-up (Figure). The crude effect of treatment allocation with enalapril was significantly related to a reduced risk of developing cardiac cachexia: RR 0.81 (95% confidence interval: 0.70 to 0.95),  $p=0.0085$ . Treatment allocation to enalapril had a significantly beneficial effect on survival independently of the effect of age, gender, NYHA class, and LVEF also in this subset of patients of the SOLVD treatment trial ( $p<0.01$ ). When we adjusted also for the presence of cardiac cachexia ( $\geq 6.5\%$  weight loss) at 4 or 8 months, the treatment effect remained significant. In patients who developed weight loss  $\geq 7.5\%$  at any time point, only 10 patients with subsequently recorded weights equal to or higher than the baseline weight were found (enalapril group: 6, placebo: 4).

### **DISCUSSION**

This report has demonstrated that significant weight loss, i.e. cardiac cachexia, is a frequent event in CHF patients. Weight loss  $\geq 7.5\%$  occurs in about 1/3 of patients over 3 years. Spontaneous reversal of the weight loss is a very rare event occurring in less than 2% of cases. Cardiac cachexia is closely and independently linked to impaired survival of CHF patients.

Treatment with an angiotensin converting enzyme inhibitor, enalapril, in addition to conventional therapy reduced the frequency of the risk of death and the risk of developing cardiac cachexia. Overall, enalapril therapy reduced the risk of developing cardiac cachexia by 19%.

It can be estimated that treatment with enalapril delayed the development of cardiac cachexia by about 7 months during the first 3 years. Interestingly, from the SOLVD treatment trial [15] it can be estimated that enalapril delayed the occurrence of death events on average by 5.4 months. A precise estimate of the proportion of the survival benefit of enalapril that was mediated through its benefit on the occurrence of body wasting is not possible to quantify, but the results of the statistical analyses show that at least some of the mortality benefit of angiotensin-converting enzyme inhibitors is mediated through the prevention or delay of cardiac cachexia.

This is the first study to analyse the frequency and degree of weight loss in CHF patients in relation to a therapeutic intervention (not considering studies with diuretics in edematous patients), and therefore we can not compare the preventive effect of enalapril on cardiac cachexia to results of other published studies. Spontaneous reversal of cardiac cachexia seems to be a very rare observation. In our own experience with about 50 patients with cardiac cachexia, we observed only of one case of spontaneous weight gain and long-term survival, and 3 cases of long-term weight stability and survival (>4 years). From clinical experience it is known that cardiac cachexia can be reversed after heart transplantation or implantation of left ventricular assist devices, but this has never been studied in detail. The present study is only the second study to analyse weight loss frequency and its prognostic impact. Previously [4] we have reported that cachectic patients with >7.5% weight loss occur with a cross-sectional frequency of 16.4%, compared to the 15 to 17% seen after 2 to 3 years in this report. With respect to cross-sectional frequency of cachexia, and the prognostic independence (from age, LVEF, and NYHA class) the present much larger multi-center study confirmed our previous findings.

In the present study population 30% of all deaths occurred on the background of newly developed cardiac cachexia - this is in a population where patients were considered clinically stable and non-cachectic at baseline. We have estimated that in our previously studied population [4] with 16.4% prevalence of cardiac cachexia at baseline nearly 50% of all deaths over a period of 18 months were related to body wasting [18]. Previous large randomised treatment trials in CHF patients did not assess the history of weight loss at baseline, have not reported weight changes over time, excluded patients with significant weight changes during the stabilisation period (V-HeFT II), or did not even report body weight at baseline [19]. Body height and body mass index are reported only rarely. Also in the SOLVD studies height has not been recorded - therefore this study reports only on absolute weight changes within patients, that are thought to be the core characteristic of the wasting disease.

Originally, treatment with angiotensin converting enzyme inhibitors has been introduced on the basis of hemodynamic considerations [20], although it was then also suggested that vasodilators per se do not have independent prognostic value, but rather that ACE inhibitors appear to be beneficial [21] perhaps via their neurohormonal antagonistic effects. The smallest randomised controlled trial of drug treatment in CHF patients with adequate power and positive mortality results was the CONSENSUS study [22], with 253 patients in NYHA class IV and a mean follow-up of only 188 days, where cenalapril caused a mortality risk reduction of 27% (p=0.003). In this study body weight at baseline was about 11 kg lower than in the present study - cachexia may have been relatively frequent in these patients. It could be hypothesised that due to metabolic effects angiotensin converting enzyme inhibitors have most powerful effects in patients with particularly advanced heart failure and in patients at risk of developing cachexia. In this context it is important that it has been noted that a significant survival benefit of patients with CHF treated with angiotensin converting enzyme inhibitors is only seen in patients with increased catecholamine levels [12,13]. Raised catecholamine levels are not only a prominent feature of cachectic CHF patients [14], but they can also contribute to upregulation of resting metabolic rates [23], that have been found in CHF patients [24].

Cardiac cachexia forms a distinct metabolic disease developing on the background of heart failure. Prevention of cachexia by treatment with the angiotensin converting enzyme inhibitor, enalapril, may indicate an important mode of action of this drug and may illustrate the importance of metabolic pathways for the progression of heart failure for its optimum therapy.

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The invention includes a method of treating a patient who has or who is at risk of cachexia the method comprising administering to the patient an effective amount of an inhibitor of the renin-angiotensin system (RAS). Such inhibitors include, but are not limited to, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor (particularly ATII) antagonists. Both of these classes of inhibitors are well known in the art and some of them are listed for example in the latest edition of the British National Formulary and in the latest edition of Martindale's Pharmacopeia.

ACE inhibitors include alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, fosinopril, lisinopril, moexipril, and the like. A particularly preferred ACE inhibitor is enalapril. Angiotensin receptor antagonists include candesartan, eprosartan, losartan, valsartan and the like. A particularly preferred angiotensin receptor antagonist is losartan.

The RAS inhibitor is administered to the patient in any suitable form and in a dose which has the desired effect of reducing or preventing cachexia.

The invention also includes the use of a RAS inhibitor in the manufacture of a medicament for treating or preventing cachexia.

Cachexia may be due to underlying disease, and it may be useful to treat the patient for the underlying disease as well as treating the cachexia according to the invention. Underlying diseases which may lead to cachexia include, for example, AIDS, liver cirrhosis, chronic obstructive pulmonary disease with or without emphysema, chronic renal failure, chronic infections (like pneumonia), cancer, heart disease including hypertension and chronic heart failure and idiopathic cachexia.

sample:

Exemplification of treatment of cachexia patients with an AT II receptor antagonist (Losartan).

(renin - angiotensin system)

We propose that the blockade of the RAS is of benefit for cachectic patients - even if such patients are previously treated with an ACE inhibitor. To exemplify this, we have treated 1 patient with cachexia due to chronic heart failure (CHF) (age 74 years, male, weight 50.0 kg, height 178 cm, previous weight loss 15.3 kg in 3 years = chronic weight loss) and 1 patient with CHF and a muscle myopathy suffering from idiopathic cachexia (age 38 years, male, weight 62 kg, height 180 cm, previous weight loss 11 kg in 1 year = recent weight loss) with Losartan (50 mg once daily) and we have studied clinical status and parameters of body composition, strength and treadmill exercise capacity at baseline and during follow-up. Both patients had evidence of CHF with impaired exercise capacity and impaired left ventricular function (LVEF <40%). Both patients had a good compliance.

Used Methods:

1. Bioelectrical impedance analysis (patient 1 and 2) was performed in the erect position using a body fat analyser (TANITA TBF-305, Tanita Corporation, IL, USA). Lean and fat mass were automatically analysed based on equations supplied and programmed into the machine by the manufacturer. These equations are based upon a comparison with measurements in a healthy population.
2. Dual energy x-ray absorptiometry (DEXA) (patient 1): Whole body DEXA-scans were performed in the Royal Brompton Hospital, London using a Lunar model DPXIQ total body scanner (Lunar Radiation Company, Madison, WI, USA, Lunar system software version 4.3c). The subject was at each time point scanned rectilinearly from head to toe. A scan takes less than 20 min. The mean radiation dose per scan is reported to be about  $0.75 \mu\text{Sv}$  [<sup>1</sup>], about 1/50th of a normal chest x-ray. The DEXA method can be used to obtain from body density analyses values of fat tissue mass, lean tissue mass. The technical details of DEXA, performance and segment demarcation have been described by Mazess et al [<sup>2,3</sup>]. The error of lean tissue measurements is <2% and of fat tissue measurements <5% [<sup>4</sup>].
3. Treadmill exercise test (patient 1 and 2): The patients underwent symptom limited treadmill exercise testing. A standard Bruce protocol with the addition of a "stage 0" consisting of 3 min at a speed of 1 mile per hour with a 5% gradient was used. The patients breathed through a one-way valve connected to a respiratory mass spectrometer (Amis 2000, Odense, Denmark) and minute ventilation, oxygen consumption and carbon dioxide production were calculated on line every 10 seconds using a standard inert gas dilution technique. Patients were encouraged to exercise to exhaustion. Exercise time and oxygen consumption at peak exercise adjusted for total body weight (peak  $\text{VO}_2$  in  $\text{ml/kg/min}$ ) were measured as an index of the exercise capacity.
4. Assessment of quadriceps muscle strength (patient 1 and 2): The subjects were seated in a rigid frame, with the legs hanging freely. An inelastic strap attached the ankle to a pressure transducer. The recording (Multitrace 2, §, Jersey, Channel Islands) from the pressure transducer was used to

assess strength and to provide visual feedback to the subject. A plateau of maximum force production indicated that the contraction was maximal. The best of three voluntary contractions on each leg, with a rest period of at least one minute in-between, was taken to represent the maximal voluntary quadriceps muscle strength of the right and left leg, respectively.

### Results

The results are summarised in Table 1. We have data available on a follow-up of 126 days in patient 1 and 83 days in patient 2. Both patient were also studied at intermediate time points. Both patients improved during treatment by 1 NYHA symptom class. In both patients the exercise capacity improved during the study (exercise time: patient 1 and 2, peak  $VO_2$ : patient 2). There was evidence that in both patients quadriceps muscle strength improved in both legs. These clinical benefits were achieved on the background on a weight gain of 4.6 kg in patient 1 (lean and fat tissue gain), and by stopping the process of weight loss and apparently improving the general clinical status and relative muscle performance, i.e. muscle quality (patient 2). We observed no side effects of treatment.

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**Example: Treatment of a hypertensive patient with some weight loss previously**

When the patient was assessed on 27 March 1998 (no ACE inhibitor) he weighed 74.6kg and had no oedema.

When assessed on 18 September 1998 following treatment with an ACE inhibitor he weighed 76.1 kg.

This shows that an ACE inhibitor can increase body weight in hypertensive patients besides their effect on lowering blood pressure.

A similar result was found in a second patient.

ANKUR

Table 1

NYHA - New York Heart Association clinical classification  
of disease

Patient	Study date	time point	age (years)	NYHA class	peak VO <sub>2</sub>	exercise (min)	strength (kg)	strength (kg)
1	02/06/98	baseline	74	4	(mL/kg/min)	(seconds)	(Newton)	(Newton)
1	11/06/98	9	4					
1	24/06/98	22	4					
1	14/07/98	42	1 to 4		8.2	64	147.15	153.41
1	25/08/98	64	1 to 4		3.0	138	223.52	229.73
1	06/10/98	126	3	Machine broken - patient clinically much improved			199.27	214.59
2	09/07/98	baseline	38	3	14.4	319	65.30	78.22
2	26/08/98	44	2		15.8	319	124.91	109.67
2	30/09/98	63	2		17.9	305		
1	14/07/98	42						
1	25/08/98	64						
1	06/10/98	126						
Patient	Study date	time point	DEXA lean kg	DEXA fat kg	Body weight	Fat %	Fat Mass (kg)	Lean Mass (kg)
1	02/06/98	baseline	44.112	2.468	5.1	50.00	1 %, TANITA measurement not possible	TANITA
1	11/06/98	9				50.00	1.0	TANITA
1	24/06/98	22	45.617	3.291	6.7	51.80	2.2	
1	14/07/98	42				53.00	3.6	
1	25/08/98	64				52.60	3.1	
1	06/10/98	126	46.552	4.937	9.2	54.80	3.8	
2	09/07/98	baseline				62.00	6 TANITA performed	
2	25/08/98	44				62.20	11.5	55.0
2	30/09/98	63				63.30	10.5	54.6

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## Table 2

Table 13. Baseline characteristics

N	2082	Survival status		Treatment group		Cachexia	
		Alive	Dead	Enalapril	Placebo	No	Yes
Gender							
Female	375 (18.0)	261 (19.7)	114 (15.1)†	183 (17.3)	192 (18.7)	227 (15.9)	148 (22.5)‡
Male	1707 (82.0)	1065 (80.3)	642 (84.9)	872 (82.7)	835 (81.3)	1198 (84.1)	509 (77.5)‡
Age	60.3	59.7	61.4‡	60.1	60.5	59.9	61.2‡
Weight	78.7	79.4	77.2‡	78.9	78.4	77.8	80.5‡
NYHA							
I	254 (12.2)	186 (14.0)	68 (9.0)†	192 (12.5)	122 (11.5)	181 (12.7)	73 (11.1)
II	1225 (58.7)	824 (62.1)	399 (51.8)	619 (58.7)	604 (58.8)	852 (59.8)	371 (56.5)
III	582 (28.0)	308 (23.2)	274 (36.2)	293 (27.8)	289 (28.1)	378 (26.5)	204 (31.1)
IV	23 (1.1)	8 (0.7)	15 (2.0)	11 (1.0)	12 (1.2)	14 (1.0)	9 (1.4)
EF							
> 25	1013 (48.7)	712 (53.7)	301 (39.8)†	511 (48.4)	502 (48.9)‡	687 (48.2)	326 (49.6)
≤ 25	1069 (51.3)	614 (46.3)	435 (60.2)	544 (51.6)	523 (51.1)	738 (51.8)	331 (50.4)
Diuretic							
No	332 (15.9)	234 (17.6)	98 (13.0)†	164 (15.5)	168 (16.4)	249 (17.4)	84 (12.8)†
Yes	1750 (84.1)	1092 (82.4)	638 (87.0)	891 (84.5)	859 (88.6)	1177 (82.6)	573 (87.2)
Antihypertensive							
No	1374 (65.0)	844 (63.7)	530 (70.1)†	708 (67.1)	666 (64.8)	930 (65.3)	444 (67.7)
Yes	708 (34.0)	482 (36.3)	226 (29.9)	347 (32.9)	361 (35.2)	495 (34.7)	213 (32.4)
Vasodilator							
No	954 (45.8)	623 (47.0)	331 (43.8)	502 (47.6)	452 (44.0)	634 (45.9)	300 (45.7)
Yes	1128 (54.2)	703 (53.0)	425 (56.2)	553 (52.4)	575 (56.0)	771 (54.1)	357 (54.3)
Etiology of HF							
Ischemic	1497 (72.0)	949 (71.7)	543 (72.6)	741 (70.2)	756 (73.8)	1023 (71.8)	474 (72.4)
Non-ischemic	582 (28.0)	375 (28.3)	207 (27.4)	314 (29.8)	268 (26.2)	401 (28.2)	181 (27.6)
Cachexia							
No	1425 (68.4%)	892 (67.3%)	533 (70.5%)	741 (70.2%)	684 (66.6%)	--	--
Yes	657 (31.6%)	434 (32.7%)	223 (29.5%)	314 (29.8%)	343 (33.4%)		

\* p ≤ 0.05. † p ≤ 0.01, ‡ p ≤ 0.001

For Tab-3

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Table 3. Effect of Cachexia on Survival. Cachexia was assessed at 4 months of follow-up.

% weight loss (at least)	Risk Ratio RR	95% CI	p
2.5 †			
Crude	1.29	(1.10, 1.50)	0.0016
Adjusted‡	1.28	(1.10, 1.49)	0.002
5.0			
Crude	1.35	(1.05, 1.75)	0.021
Adjusted	1.41	(1.10, 1.81)	0.006
7.5			
Crude	1.77	(1.20, 2.60)	0.004
Adjusted	2.08	(1.45, 2.99)	0.00007
10.0			
Crude	1.57	(0.85, 2.91)	0.15
Adjusted	1.70	(0.92, 3.16)	0.092
15.0			
Crude	9.08	(5.25, 15.7)	< 0.0001
Adjusted	8.78	(4.83, 15.95)	< 0.0001

† Cut-point for the definition of Cachexia at 4 months

‡ Adjusted for age, treatment, gender, NYHA and ejection fraction

Increased risk of death with increased cachexia

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Table 3

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Table 4. Effect of Cachexia on Survival. Cachexia was assessed at 8 months of follow-up.

% weight loss (at least)	Risk Ratio RR	95% CI	P
2.5 †			
Crude	1.22	(1.04, 1.43)	0.014
Adjusted‡	1.21	(1.04, 1.42)	0.02
5.0			
Crude	1.42	(1.14, 1.76)	0.002
Adjusted	1.47	(1.18, 1.82)	0.0005
7.5			
Crude	1.66	(1.22, 2.26)	0.001
Adjusted	1.74	(1.28, 2.38)	0.00004
10.0			
Crude	1.62	(1.00, 2.63)	0.049
Adjusted	1.83	(1.14, 2.94)	0.013
15.0			
Crude	2.24	(0.96, 5.23)	0.062
Adjusted	2.53	(1.10, 5.83)	0.030

† Cut-point for the definition of Cachexia at 8 months

‡ Adjusted for age, treatment, gender, NYHA and eGFR

Increased risk of death with increased cachexia

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Table 13. Effect of Cachexia on Survival. Cachexia was assessed at each follow-up visit.

	RR	95% CI	P
Cachexia†	1.41	(1.23, 1.63)	<0.0001
Age	1.02	(1.01, 1.02)	<0.0001
Treatment	1.11	(0.96, 1.28)	0.170
Gender	1.34	(1.09, 1.65)	0.006
NYHAII	1.30	(0.99, 1.70)	0.06
NYHAIII	1.84	(1.39, 2.43)	<0.0001
NYHAIV	2.17	(1.33, 3.55)	0.002
EF	1.44	(1.23, 1.67)	<0.0001

† A 6.5 cut-point is used for the definition of Cachexia

Shows risk factors and their relation  
to predicting death independently of each other

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Shows frequency of developing cardio cachexia over time in patients treated with

enalapril compared to patients treated with placebo

Cumulative Risk of Cachexia -- 5.0

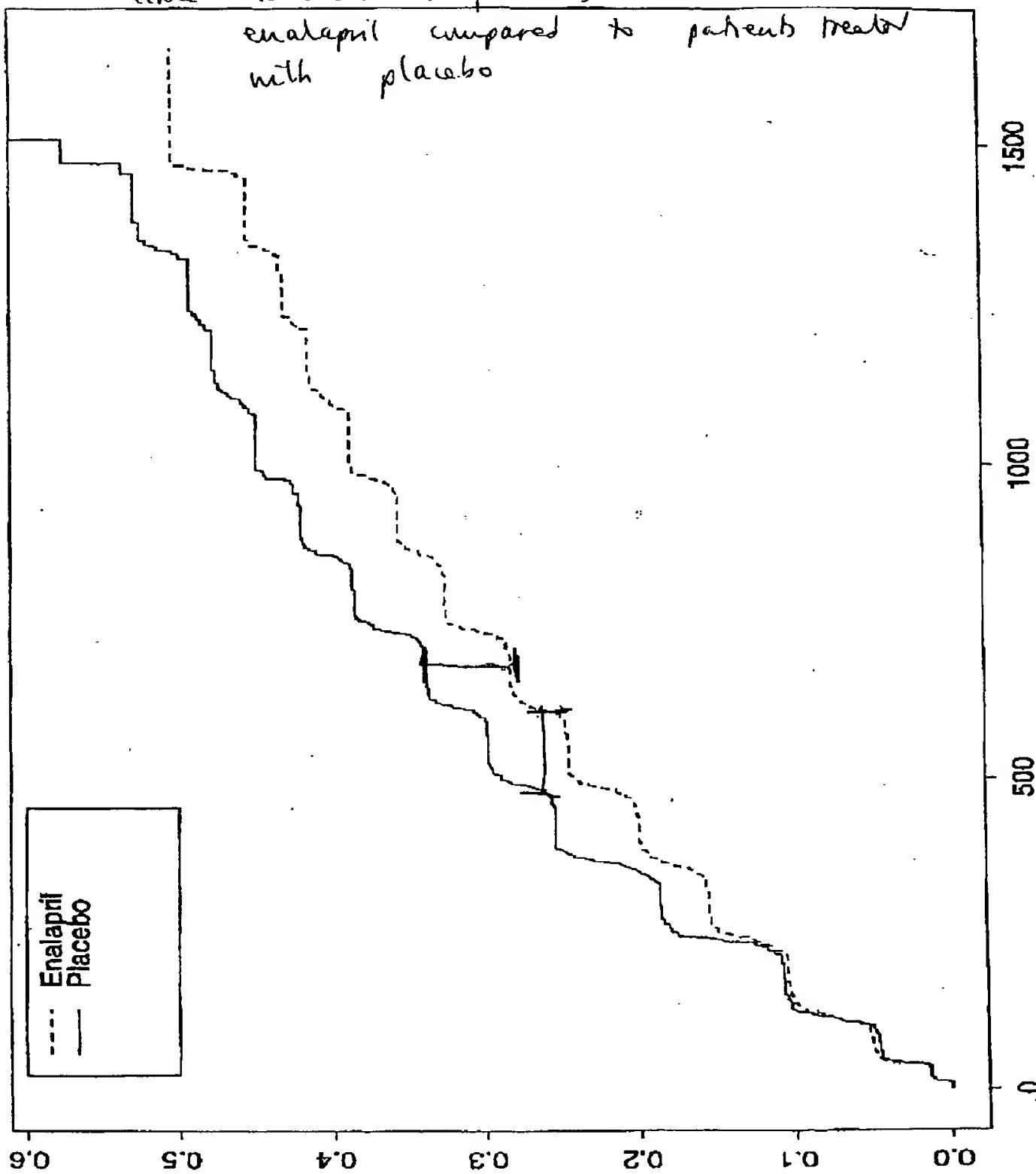


Figure 1

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Cumulative Hazard -- 6.5

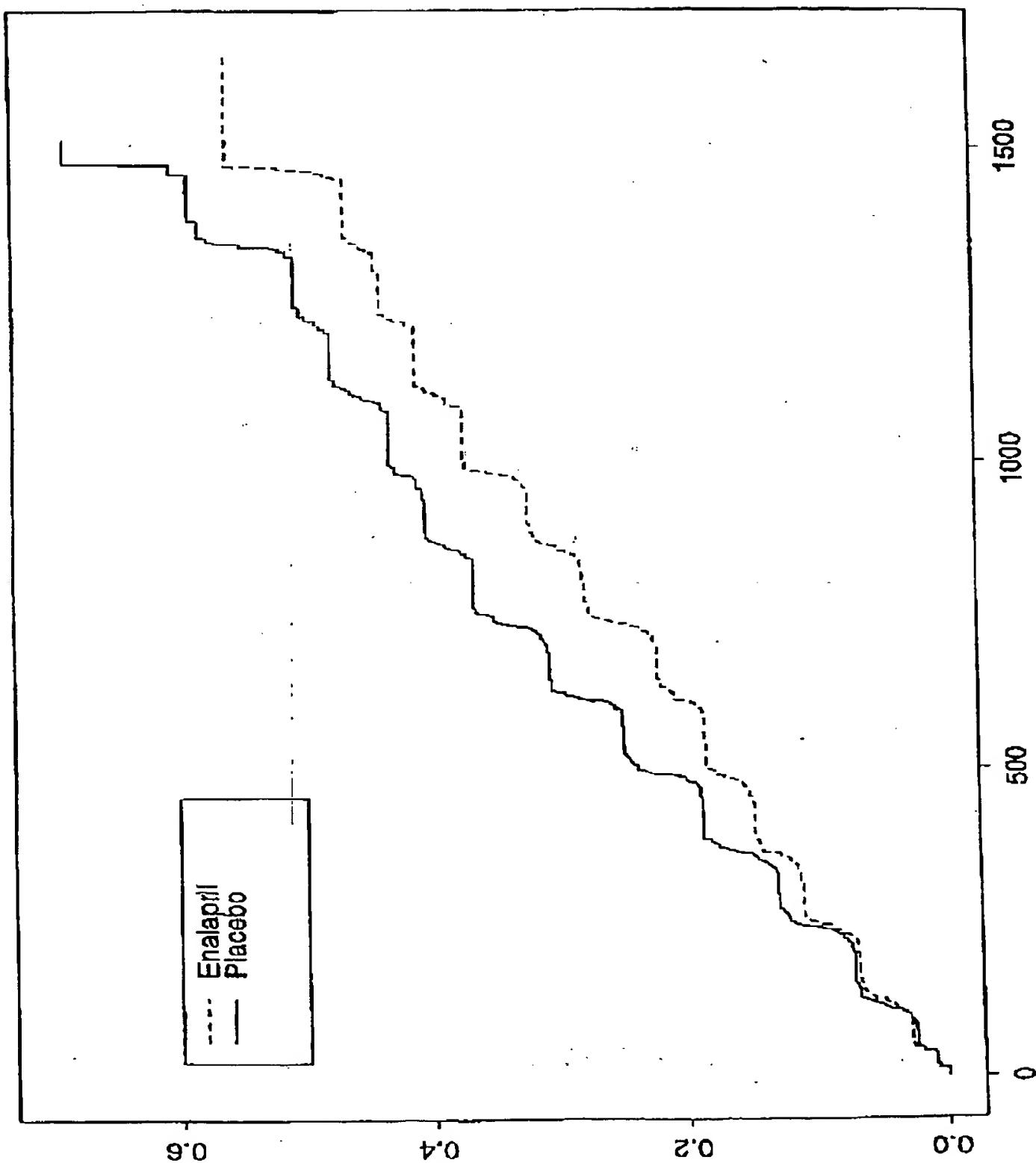


Figure 2  
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Cumulative Risk -- 6.5

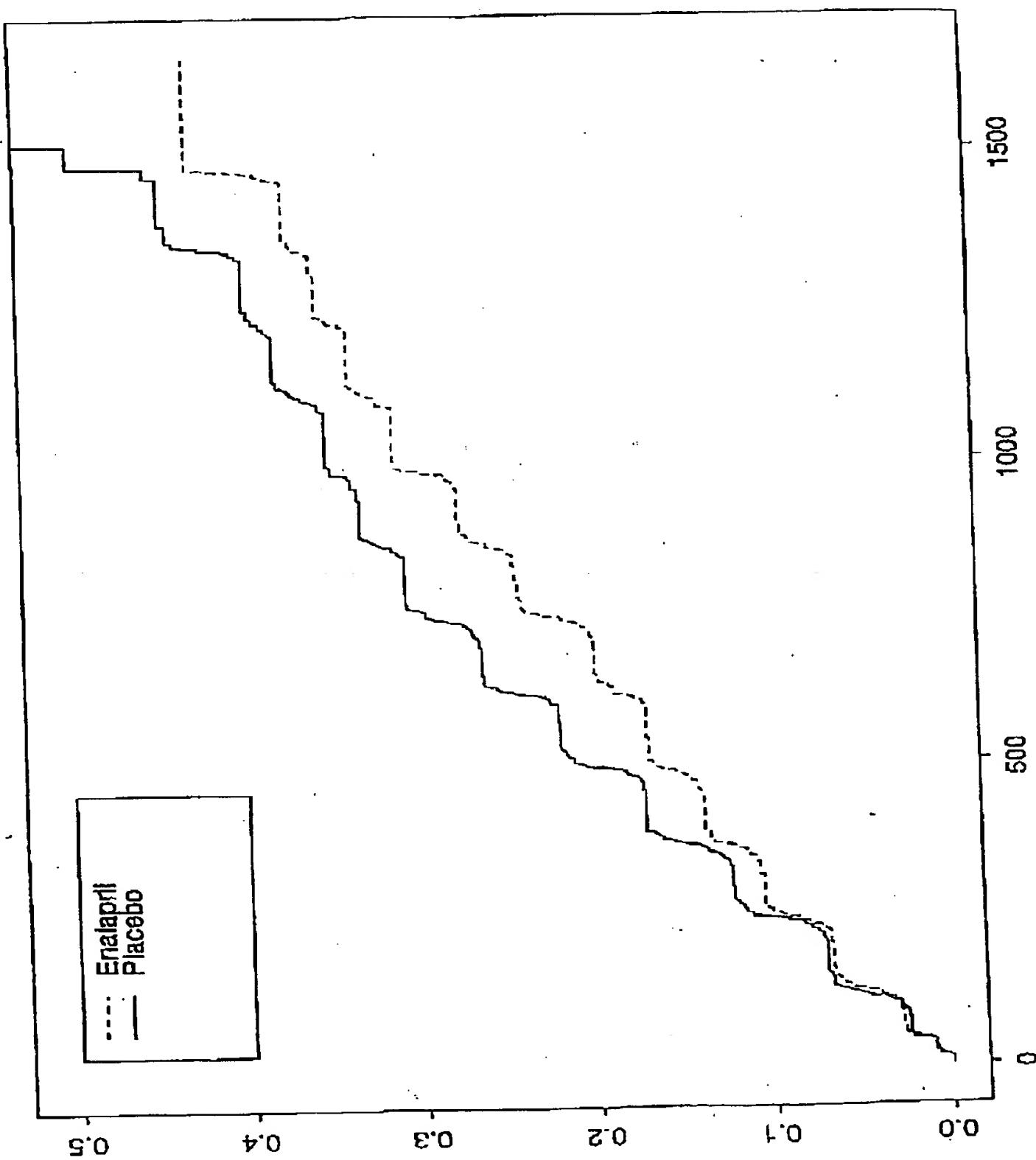


Figure 3

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Cumulative Risk of Cachexia 7.5'

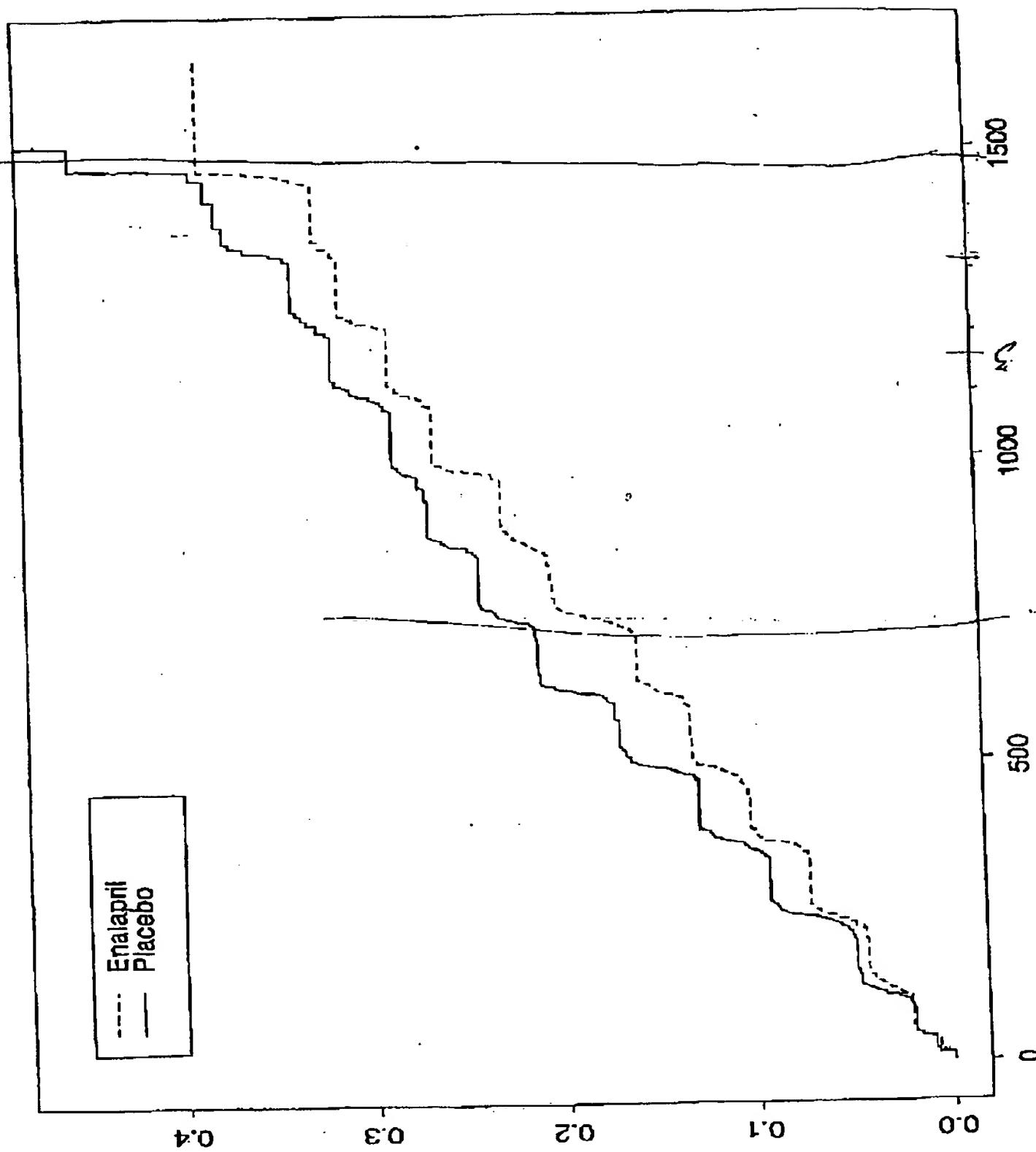


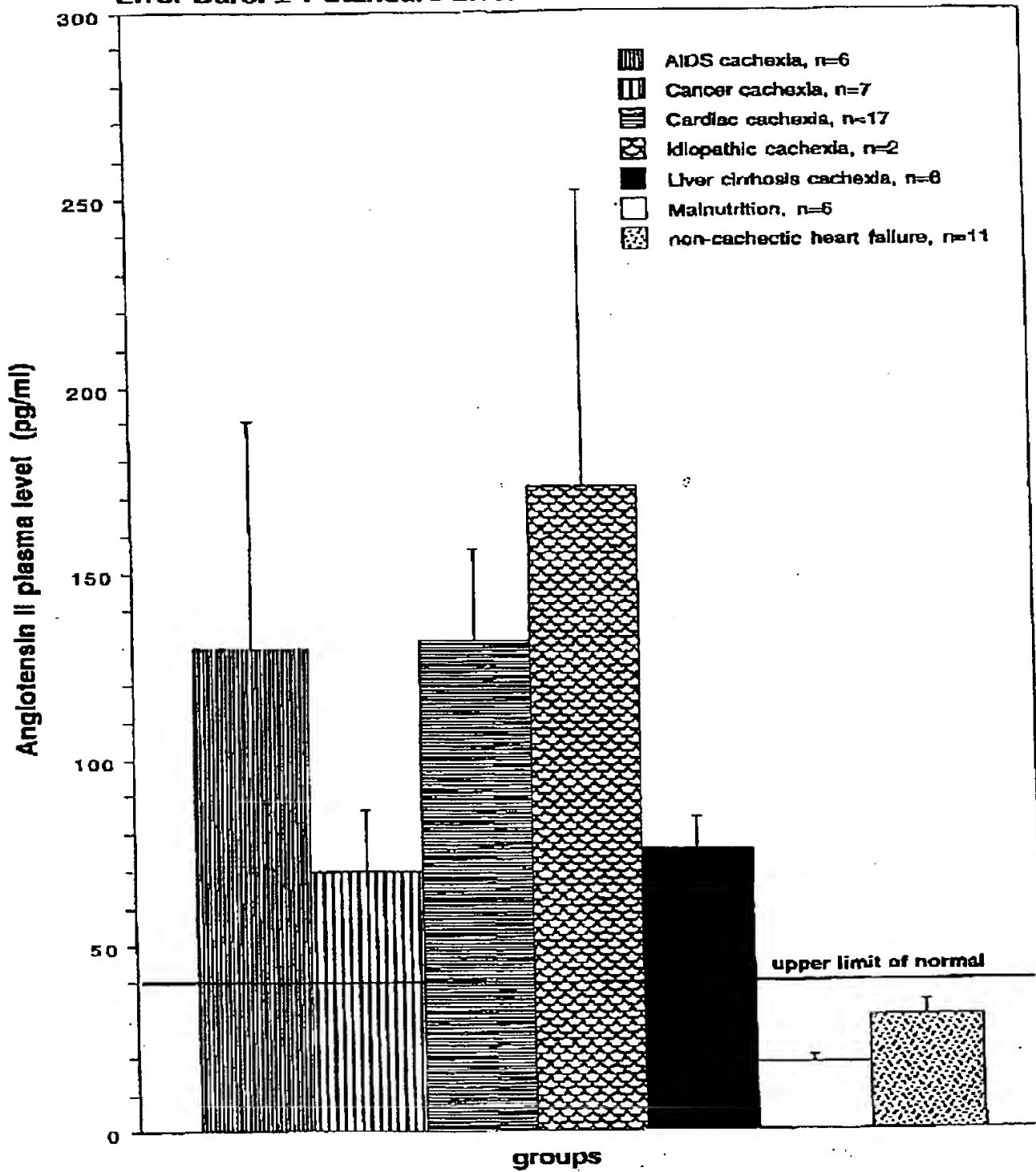
Figure 4

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Angiotensin II plasma levels  
in various patient types

Cell Bar Chart

Split By: diagnosis

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Patients with wasting disease have increased  
angiotensin II plasma levels.

Figure 5 5/5

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Eric Potter  
Clarkson

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